A STUDY OF THE CHEMISTRY OF INDAZOLE

BY

CRAYTON BEVILLE THOMPSON

B.S., University of Texas, 1942
M.S., University of Illinois, 1947

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
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Introduction

Indazole, 4,5-benzopyrazole, bears a close structural resemblance to indole. Since many derivatives of indole are important biochemically, it would be of great interest to study the physiological properties of a number of indazole compounds; those of particular interest are substances related to natural indole derivatives, but with the indole system replaced by the indazole group.

Very little attention has been devoted to the chemistry of indazole by previous investigators. The purpose of the present work was to extend the knowledge of the reactions of the substance and to develop methods of synthesis which might be applicable to the preparation of the indazole analog of tryptophan.

Discussion Of Results

Although indazole is structurally similar to indole, it is not nearly so active chemically. Indazole, N-benzylindazole and 5-nitroindazole failed to undergo the Mannich reaction (1) under even the most vigorous conditions. Attempts at chloromethylation, formation of the Grignard reagent and reaction with diazoacetic ester were unsuccessful.

An analog of tryptophan was prepared *via* the following reaction sequence: isatin, 3-indazolecarboxylic acid (2), the methyl ester, the piperidide, 3-piperidinomethylindazole, the methiodide, ethyl α-acetamido-α-carbethoxy-β-(3-indazole)-propionate (3), α-amino-α-carboxy-β-(3-indazole)-propionic acid to α-amino-β-(3-indazole)-propionic acid. An alternative procedure involved conversion of 3-indazolecarboxylic acid to the acid chloride and the N,N-dimethylamide, which was reduced by lithium aluminum hydride to 3-dimethylaminomethylindazole (4), which formed a methiodide that alkylated acetamidocyanoacetic ester. Hydrolysis of the alkylation

product gave the amino acid. 3-Piperidinomethylindazole was not an effective alkylating agent for acetamidomalonic ester or for nitromalonic ester.

Several procedures were followed in an attempt to prepare 3-indazolealdehyde. Treatment of indazole with N-methylformanilide and phosphorus oxychloride, the McFadyen-Stevens reaction (5) with the methyl ester of 3-indazolecarboxylic acid and a modification of the Sommelet reaction with the Mannich base were not successful. 3-Chloroindazole did not undergo the Rosenmund-von Braun reaction to form the nitrile, an intermediate in the Stephens synthesis of aldehydes.

Lithium aluminum hydride reduction of the methyl ester of 3-indazolecarboxylic acid produced 3-hydroxymethylindazole. No useful way was found to convert this product into 3-bromo- or 3-chloromethylindazole, other alkylating agents for acetamidomalonic ester in the synthesis of amino acids.

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VITA

The author was born on December 28, 1920, in Paris, Texas, where he received his elementary and high school education. He entered Paris Junior College in September, 1937, and was graduated in June, 1939. In September of that year he enrolled in the University of Texas, from which institution he received the degree of Bachelor of Science in Chemical Engineering in June, 1942. He was employed by the Freeport Sulphur Company until March, 1943. He served in the United States Army Air Corps from 1943 to 1946. In June, 1946, he entered the Graduate College of the University of Illinois, and he received the Master of Science degree in June, 1947. He held a part-time teaching assistantship from September, 1947 until June, 1949.

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